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Impact of parvovirus B19 infection on paediatric patients with haematological and/or oncological disorders

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Abstract

To determine the frequency and the impact of parvovirus B19 (B19V) infection and its influence on the course of haematological and/or oncological diseases in paediatric patients, consecutive serum and bone marrow samples from 110 were analyzed for markers of acute, past and persistent B19V-infection using qPCR, ELISA and WesternLine. Twenty-seven out of 110 (24.5%) children suffered from non-malignant diseases (anaemia, pancytopenia, autoimmune disorders); 68/110 (61.8%) patients had developed leukaemia, malignant lymphoma or solid malignant tumours; 15/110 patients (13.6%) presented with other symptoms. At admission, B19V-specific IgM and IgG indicating acute or previous B19V-infection were observed in 5 (4.5%) and 48 patients (43.6%), respectively. B19V-DNA (10^3–10^9 geq/mL) was detectable in serum and/or bone marrow of 22 patients (20.0%). These suffered from leukaemia (5), non-Hodgkin lymphoma (2), solid tumours (6), autoimmune (4) and haematological (4) disease and fever (1). During clinical observation four further leukaemia patients developed viraemia and persistent B19V-infection was observed in 13/22 DNA-positive patients. Treatment of B19V-DNA-positive cancer patients was associated with more supportive therapy involving erythrocyte and thrombocyte transfusion and/or antibiotic therapy. Acute B19V-infection has been frequently observed in paediatric patients with haematological and/or oncological disease. In patients with non-malignant diseases anaemia or autoimmune disorders were diagnosed in association with B19V-infection. Furthermore, a significant number of cancer patients displayed markers for acute, recent or persistent B19V-infection. This association may be strengthened by frequent treatment with blood products combined with therapeutic immune suppression. In B19V-infected cancer patients supportive therapy was more complex.

Keywords: Haematological disease, leukaemia, oncological disease, parvovirus B19, persistence
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Introduction

Parvovirus B19 (B19V) is the aetiological agent of erythema infectiosum, a childhood rash disease, and of a wide spectrum of further diseases [1,2]. Due to the destruction of erythroid precursor cells in bone marrow, the main targets for B19V replication, the patients develop anaemia, resulting in haematopoietic disorders (e.g. transient red cell aplasia, thrombocytopenia and pancytopenia in children and adults, or hydrops fetalis in pregnant women) [3,4]. The patients may develop acute polyarthropathy, arthritis and various autoimmune disorders [5,6]; hepatitis, myocarditis, myositis, vasculitis and encephalitis are observed rarely.

Acute B19V-infection is characterized by high viraemia and the presence of viral genomes in the bone marrow. As parvovirus particles are extremely resistant to detergents and environmental influences, both iatrogenic and nosocomial transmission may occur, mainly by respiratory secretions but also by blood and blood products. This presents a particular risk for therapeutically immunosuppressed children with haematological and/or malignant diseases, which may establish persistent infection associated with long-lasting haematological symptoms. Acute and persistent B19V-infection has been shown to need enhanced supportive treatment and lead to

complications in children with acute lymphoblastic leukaemia (ALL) or Hodgkin-lymphoma, with the consequence of more erythrocyte transfusions and extended hospitalization [7–10].

We determined the impact of B19V-infection on the disease course of 110 paediatric patients of a haemato-oncological ward, hospitalized with haematological and oncological disorders including solid malignant tumours. We analysed consecutive serum and bone marrow samples for markers indicating acute, past and persistent B19V-infection and correlated these data with the patient's diseases and various clinical parameters.

Material and Methods

Patients

Two hundred and ninety-one serum and 112 bone marrow samples were obtained for diagnostic reasons from 110 Caucasian children and adolescents (age, 4–235 months; mean age, 93.6 months) with haematological and/or oncological diseases (65 males, 45 females). All were inpatients of a paediatric hemato-oncological ward between December 2004 and July 2007 (mean observation time, 12 months; range, 2–44 months, partially with intermission). Paired serum and bone marrow samples were taken at the time of clinical admission from enrolled patients. Some patients were included at the time point of clinical therapy and stored serum and/or bone marrow samples were analysed retrospectively. During treatment follow-up samples were available from 60/110 patients (54.5%). The clinical diagnosis was carried out according to the actual guidelines for the respective diseases and encompassed a broad spectrum including various forms of leukaemia (ALL, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS)), malignant lymphoma (morbus Hodgkin, non-Hodgkin lymphoma (NHL)), solid malignant tumours (nephroblastoma, neuroblastoma, rhabdomyosarcoma, brain tumours), and haematological (anaemia, thrombocytopenia, pancytopenia, agranulocytosis, thrombocytosis) and autoimmune disorders (Evan's syndrome, idiopathic thrombocytopenic purpura (ITP)).

According to diagnosis, patient subgroups A, B and C were formed (Table 1). Patients (27/110, 24.5%) in group A presented with non-malignant haematological diseases subclassified as autoimmune (14/110, 12.7%) and haematological diseases (13/110, 11.8%). Group B patients (68/110, 61.8%) were treated for malignancies and grouped into patients with leukaemia (31/110, 28.2%), malignant lymphoma (12/110, 10.9%) and solid tumours (25/110, 22.7%). Group C

TABLE 1. Clinical course and serological markers for B19V-infection at the time of admission

Group of patients/diagnoses	Age/months (mean)	Patients		IgG (%)			IgM (%)	Parvovirus B19 DNA (%)			
		Total	With follow-up	VP1/VP2 part[a]	VP2 den[a]	NS1	VP1/VP2	Total serum or bone marrow[b]	In Serum	In bone marrow	Serum and bone marrow[c]
Total	93.6	110	60	43.6	26.4	15.5	4.5	20.0	14.5	15.5	10.0
Group A (non-malignant)	89	27	8	40.7	33.3	22.2	7.4	29.6	18.5	29.6	18.5
Autoimmune disease	94	14	3	42.9	35.7	28.6	7.1	28.6	14.3	28.6	14.3
Evan's syndrome	152	2	2	100.0	100.0	100.0	0	50.0	50.0	50.0	50.0
ITP	79	9	0	33.3	33.3	22.2	11.1	22.2	11.1	22.2	11.1
Other	131	3	1	33.3	0	0	0	33.3	0	33.3	0
Haematological disease	77	13	5	38.5	30.8	15.4	7.2	30.8	23.1	30.8	23.1
Fanconi anaemia	82	2	2	100.0	100.0	100.0	0	100.0	50.0	100	50.0
Anaemia	63	3	1	33.3	33.3	0	33.3	33.3	33.3	33.3	33.3
Thrombocytopenia	69	4	0	50.0	25.0	0	0	25.0	25.0	25.0	25.0
Pancytopenia	104	2	0	0	0	0	0	0	0	0	0
Agranulocytosis	16	1	1	0	0	0	0	0	0	0	0
Thrombocytosis	145	1	1	0	0	0	0	0	0	0	0
Group B (malignant disease)	101	68	50	45.6	26.5	14.7	4.4	19.1	14.7	11.8	7.4
Leukaemia	92	31	24	41.9	22.6	9.7	6.5	16.1	16.1	6.5	6.5
ALL	93	24	19	41.6	16.7	4.2	4.2	16.7	16.7	4.2	4.2
AML	84	3	3	33.3	66.7	33.3	33.3	0	0	0	0
CML	120	2	2	0	0	0	0	0	0	0	0
MDS	63	2	0	100.0	50.0	50.0	0	50.0	50.0	50.0	50.0
Malignant lymphoma	119	12	8	41.7	33.3	16.7	0	16.7	0	16.7	0
Hodgkin	132	3	3	33.3	66.7	33.3	0	0	0	0	0
Non-Hodgkin	113	9	5	44.4	22.2	11.1	0	22.2	0	22.2	0
Solid tumours	103	25	18	52.0	28.0	20.0	4.0	24.0	20.0	16.0	12.0
Neuroblastoma	62	6	5	50.0	16.7	0	0	16.7	0	16.7	0
Nephroblastoma	50	2	1	50.0	50.0	50.0	0	50.0	50.0	0	0
Rhabdomyosarcoma	131	3	2	100.0	33.3	33.3	33.3	66.7	66.7	66.7	66.7
Brain tumour	154	7	6	71.4	57.1	42.9 0	0	28.6	28.6	14.3	14.3
Other tumours	91	7	4	14.3	0	0	0	0	0	0	0
Group C (other diseases)	70	15	2	40.0	13.3	6.7	0	6.7	6.7	6.7	6.7

[a]Part, particulate antigen; den, denatured antigen.
[b]Patients with B19V-DNA present in either serum or bone marrow.
[c]Patients with B19V-DNA present in both serum and bone marrow.

encompassed patients (15/110; 13.6%) mainly suffering from unclear fever and abnormalities in blood counts, who were hospitalized for diagnostic reasons (i.e. to exclude underlying malignancies). With the exception of patients with solid tumours (68.0% males), the female to male ratio was balanced. Patients with follow-up samples were coded by Arabic numbers (1,2,3) whereas Roman numbers (I, II, III) were used for patients without follow-up samples.

Detection of B19V-specific antibodies and B19V-DNA

To determine seroprevalence, all sera were screened for B19V-specific IgG and IgM against VP1-proteins (VP1-*unique region*) and virus-like VP2-particles (VP1/VP2part) by ELISA (Recom*Well*; Mikrogen GmbH, Neuried, Germany). IgG- and/or IgM-positive sera were further analysed by WesternLine (RecomLine; Mikrogen GmbH) for antibodies against virus-like VP2-particles (VP2part), and denatured VP2- (VP2den), VP1- (VP1-*unique region* and the aminoterminal VP1-region, amino acids 1–499) and NS1-proteins. In general, IgG against denatured VP2-proteins and epitopes is detectable together with antibodies against VP2-particles in individuals with recent B19V-infection having occurred up to 6 months before testing [11–13]. NS1-specific IgG is frequently observed several weeks following acute infection in cases with prolonged viraemia or in patients who develop persistent B19V-production [5,14,15].

DNA was isolated from 200 μL of each serum or bone marrow sample using the QIAamp Blood kit (Qiagen, Hilden, Germany). Each preparation (100 μL final eluate) was used immediately or stored at −20°C. B19V-DNA was detected in duplicate assays using the quantitative real-time TaqMan PCR assay established for joint amplification of B19V genomes, genotypes 1–3 [16]. Results were considered as positive if viral nucleic acids were detected in both assays. For values indicative of low-level DNAemia ($<1 \times 10^3$ geq/mL) defined numbers were not used due to test-specific deviations. Further specification of individual genotypes was not performed.

Statistics

For statistical analysis, the chi-square test was applied to compare proportions.

Results

With respect to all patients, a seroprevalence of 43.6% (48/110) was observed at admission, as demonstrated by VP1/VP2part-specific IgG (Table 1). In 22/110 (20%) children B19V-DNA was detected in serum and/or bone marrow, with B19V-specific IgM detectable in five of these patients, confirming acute infection. Twenty-nine out of 110 children (26.4%) displayed IgG against VP2den, indicating recent B19V-infection. NS1-specific IgG was observed in 17/110 (15.5%) children.

Patients with non-malignant diseases (group A)

Seroprevalence was 40.7% (11/27) in patients with non-malignant diseases (Table 1). VP2den- and NS1-specific IgG was detectable in 9/11 (81.8%) and 6/11 (54.4%) seropositive children. On admission, B19V-DNA (10^2–10^3 to 7.6×10^6 geq/mL) was present in serum and/or bone marrow of eight out of eleven (72.2%) seropositive children (patients AI-AIV, A1–A4) and three out of eight DNA-positive patients (A2–A4) displayed B19V-genomes also in follow-up samples (Table 2). Persistent viraemia was observed in patient A2 (Fanconi anaemia) for 11 months. During the average observation of 21 months, none of the IgG-negative patients showed seroconversion or markers for acute B19V-infection.

Autoimmune disease. All seropositive patients (42.9%; 6/14) displayed markers for acute and/or recent B19V-infection: VP2den-specific IgG was present in combination with B19V-DNA in bone marrow and/or serum samples of patients AI (Evan's syndrome), AI and AII (both ITP) and AIII (Kawasaki disease); in patient AII, B19V-specific IgM was also detected (Table 2).

Haematological disease. Five out of 13 patients (38.5%) displayed VP1/VP2part-specific IgG (Table 1). Four out of five seropositive patients presented with acute B19V-infection (Table 2). On admission, B19V-DNA was detectable in serum and bone marrow of patients A2, A3 (both Fanconi anaemia) and A4 (aplastic anaemia), and also during 6–14 month follow-up periods. Initially, patient A4 was IgM-positive, and B19V-DNA was present in peripheral blood (1.2×10^5 geq mL) and bone marrow (7.6×10^6 geq/mL); 6 months later, the values decreased to 10^2–10^3 geq/mL serum, indicating the gradual control of viraemia. A similar situation was observed in patient A3 whereas patient A2 displayed low-levels of B19V-DNA in all available follow-up samples, despite having B19V-specific antibodies (Table 2). In combination with B19V-DNA in bone marrow, viraemia was also observed as a marker for productive B19V-infection in patient AIV presenting with thrombocytopenia.

Patients with malignant diseases (group B)

Seroprevalence was 45.6% (31/68 patients); in 18/68 (26.5%) and 10/68 (14.7%) seropositive children, VP2den- and NS1-specific IgG was detectable, respectively. At admission,

TABLE 2. Serological and clinical parameters of B19V-DNA-positive patients without (AI–AIV, BI–BVIII and CI) and with follow-up samples (A1–A4 and B1–B9)

			IgG			IgM	Viral DNA (geq/mL)		
Patient/sample number	Disease	Date (month/year)	VP1/VP2 part	VP2 den	NS1	VP1/VP2	Serum	Bone marrow	State of infection
A1/1	Evan's syndrome	04/2005	+	+	+	–	10^2–10^3	5.4×10^3	Acute/recent
A1/2		02/2006	+	–	–	–	–	n.a.	Past
A2/1	Fanconi anaemia	04/2005	+	+	+	–	–	10^2–10^3	Acute/recent
A2/2		03/2006	+	+	+	–	10^2–10^3	10^2–10^3	Persistent
A3/1	Fanconi anaemia	11/2004	+	+	+	–	10^2–10^3	2.6×10^4	Acute/recent
A3/2		05/2005	+	+		–	–	2.3×10^3	Recent
A3/3		03/2006	+	+		–	–	–	Past
A4/1	Aplastic anaemia	08/2005	–	+	–	+	1.2×10^5	7.6×10^6	Acute/recent
A4/2		02/2006	+	+	+	–	10^2–10^3	n.a.	Persistent
AI	ITP		+	+	+	–	–	10^2–10^3	Recent
AII	ITP		+	+	+	+/–	1.4×10^3	4.1×10^4	Acute/recent
AIII	Kawasaki disease		n.a.	n.a.	n.a.	n.a.	n.a.	1.6×10^3	Unclear/recent?
AIV	Thrombocytopenia		+	+	–	+	1.9×10^3	3.4×10^3	Acute/recent
B1/1	ALL	08/2006	+	–	–	–	10^2–10^3	10^2–10^3	Recent
B1/2		09/2006	+	+	–	–	–	10^2–10^3	Recent
B1/3		06/2007	+	+	–	–	n.a.	n.a.	Past?
B2/1	ALL	10/2005	+	–	–	–	–	–	Past
B2/2		10/2005	+	+	+	–	10^2–10^3	1.5×10^3	Persistent
B2/3		11/2005	+	+	+	+	10^2–10^3	10^2–10^3	Persistent
B2/4		12/2005	+	–	+	–	–	–	Past
B2/5		01/2006	+	+	+	–	–	10^2–10^3	Persistent
B2/6		02/2006	+	+	+	–	10^2–10^3	–	Persistent
B3/1	ALL	01/2005	+	–	–	–	10^2–10^3	–	Unclear/persistent?
B3/2		03/2006	+	–	–	–	–	–	Past
B4/1	ALL	02/2005	+	–	–	–	–	–	Past
B4/2		07/2005	+	–	–	–	–	10^2–10^3	Persistent
B4/3		12/2005	+	–	–	–	–	–	Past
B4/4		01/2006	+		–	–	–	–	Past
B5/1	ALL	04/2004	+	–	–	–	–	–	Past
B5/2		09/2005	+	–	–	–	–	–	Past
B5/3		10/2005	+	+	+	+	10^2–10^3	10^2–10^3	Persistent
B5/4		12/2005	+	–	–	–	–	–	Past
B5/5		03/2006	+	–	–	–	–	–	
B6/1	ALL	12/2005	–	–	–	+	6.9×10^9	n.a.	Acute
B6/2		03/2006	+	+	–	+	10^2–10^3	n.a.	Persistent
B6/3		06/2006	+	+	+	–	1.2×10^4	n.a.	Persistent
B7/1	AML	06/2006	–	+	–	+	–	–	Unclear
B7/2		07/2006	+	+	–	+	–	10^2–10^3	Unclear/persistent?
B8/1	Rhabdomyo-	05/2005	+	+	+	–	10^2–10^3	10^2–10^3	Recent/persistent
B8/2	sarcoma	03/2006	+	+	+	–	–	n.a.	Recent
B9/1	Brain tumour	05/2007	+	+	+	–	10^2–10^3	10^2–10^3	Recent/persistent
B9/2		06/2007	+	+	+	–	10^2–10^3	10^2–10^3	Recent/persistent
BI	ALL		+	+	–	–	10^2–10^3	–	Recent
BII	MDS		+	+	+	–	10^2–10^3	10^2–10^3	Recent
BIII	NHL		+	+	–	–	–	1.8×10^3	Unclear/recent?
BIV	NHL		+	+	–	–	–	10^2–10^3	Unclear/recent?
BV	Neuroblastoma		–	–	–	–	n.a.	10^2–10^3	Unclear
BVI	Nephroblastoma		+	+	+	–	2.1×10^3	n.a.	Recent/persistent
BVII	Rhabdomyosarcoma		+	+	+	–	10^2–10^3	10^2–10^3	Recent/persistent
BVIII	Brain tumour		+	+	–	–	–	10^2–10^3	Recent
CI	Fever		+	+	–	–	10^2–10^3	10^2–10^3	Recent

B19V-DNA was present in serum and/or bone marrow of 13/68 (19.1%) patients, relating to 5/31 (16.1%) leukaemia patients, 2/12 (16.6%) malignant lymphoma patients and 6/25 (24.0%) individuals with solid malignant tumours. During an average observation of 10 months, B19V-DNA became detectable in serum and/or bone marrow of four initially DNA-negative patients (B2, B4, B5 and B7; Table 2).

Leukaemia. On admission, 13/31 (41.9%) children displayed VP1/VP2part-specific IgG. Several patients displayed markers for acute/recent or persistent infection. In MDS-patient BII viraemia and VP2den-specific IgG were observed. Eight out of 27 (29.6%) ALL/AML-patients (BI, B1–B7) displayed markers for productive B19V-infection, four of these (BI, B1, B3 and B6) presented with acute/recent B19V-infection at admission and diagnosis of ALL; patients B1 and B6 were unable to control B19V-infection during the following months of chemotherapy. B19V-DNA became also detectable in follow-up samples from ALL-patients B2, B4 and B5 and AML-patient B7 (Table 2). These children were seropositive at admission, but B19V-DNA was not detectable in serum or bone marrow. They developed viraemia during treatment, and patient B2 established long-lasting virus persistence. In bone marrow of AML-patient B7, B19V-DNA was detected 32 days after initial diagnosis (Table 2).

Malignant lymphoma. At admission, 5/12 (41.6%) patients displayed VP1/VP2part-specific IgG; VP2den- and NS1-specific

IgG, respectively, were detectable in four and two of these patients (Table 1). Viral DNA was not detected in any serum sample, but in bone marrow of NHL-patients BIII and BIV (2/12, 16.6%) B19V-DNA (Table 2).

Solid tumours. At admission, 13/25 (52.0%) patients were seropositive. VP2den- and NS1-specific IgG was detectable in seven and five of the seropositive patients, respectively (Tables 1 and 2). In 6/25 (24%) patients (BV, neuroblastoma; BVI, nephroblastoma; BVII, B8, rhabdomyosarcoma; BVIII, B9, brain tumour) B19V-DNA was detected in sera and/or bone marrow. The traceability of B19V-DNA did not change during clinical observation of up to 8 months.

Patients with other diseases (group C)

Seroprevalence in patients presenting with neither non-malignant haematological nor malignant diseases was 40.0% (6/15 patients; Table 1). In combination with IgG against VP2den, B19V-DNA in serum and bone marrow of 1/15 patients (patient CI) indicated recent infection (Table 2).

Influence of B19V-infection on the therapeutic regimen of tumour patients

To study the influence of B19V-infection on clinical and therapeutic management, we compared the treatment courses of B19V-DNA-positive cancer patients (patients B1–B9) with those of 11 B19-DNA-negative tumour patients. In general, treatment was carried out in accordance with the respective guidelines [17]. In the case of severe disease progression individual treatment attempts were used. One death occurred among the B19V-DNA-positive ALL-patients: patient B5 died after 25.4 months of extensive therapy. Whereas clinical relapses led to high-dose chemotherapy with subsequent stem-cell transplantation in 33.3% of B19V-DNA-positive patients, only one B19V-DNA-negative patient (9.1%) showed this condition (Table 3). Regarding the duration and intensity of chemotherapy and treatment intervals only minor differences were observed between B19V-DNA-positive and negative tumour patients. This may be explained by the small patient numbers in both groups.

Whereas most patients were treated with erythrocyte and thrombocyte transfusions, the B19V-DNA-positive patients required more donations of both cell preparations than the B19V-DNA-negative patients. To compensate for the difference in duration of therapy, the values were adjusted to 100 days of treatment. B19V-DNA-positive treated patients required 3.4 (mean 48.9 mL/kg) erythrocyte and 3.1 thrombocyte transfusions; those numbers are in contrast to 1.9 (25.9 mL/kg) erythrocyte and 0.8 thrombocyte donations per B19V-DNA-negative treated patient, respectively (Table 3). Analysing the frequency (8.4 regular donations/100 days/B19V-DNA-positive patient vs. 3.1 donations/100 days/B19V-DNA-negative patient) and the duration (45.7 vs. 11.9 days, median) of antibiotic administration, similar relations were observed. Seronegative and seropositive patients without detectable amounts of B19V-DNA displayed only minor differences.

Discussion

We analysed serum and bone marrow samples of children with haematological and/or oncological disease for the presence of B19V-specific antibodies and viral DNA over a period of up to 44 months. On admission, an overall seroprevalence of 43.6% was observed, that was lowest in children with non-malignant haematological diseases (38.5%; mean age: 76.8 months) and highest in malignant lymphoma patients (52%; mean age, 119 months). This is in accordance with age-matched healthy European children [18,19].

Only one of six seropositive patients (16.7%) with neither haematological nor oncological disorders (group C) displayed low-level viraemia. Similar values for viraemia have been detected in healthy children and paediatric patients with

TABLE 3. Details used for treatment of B19V-DNA-positive and negative leukaemia patients

Therapeutic details

Patients	Erythrocytes			Thrombocytes		Treatment with antibiotics[a]		
	Patients with HDC+SCT	Patients treated	Donations/patient[b]	Patients treated	Donations/patient[b]	Patients treated	Donations/patient[b] treated	Duration/patient treated (days)
B19V-DNA negative	1/11 (9.1%)	10/11 (90.9%)	1.9 25.9 mL/kg bw	10/11 (90.9%)	0.8	10/11 (90.9%)	3.1	11.9
B19V-DNA positive	3/9 (33.3%)	7/9 (77.7%)	3.4 48.9 mL/kg bw	5/9 (55.6%)	3.1	7/9 (77.7%)	8.4	45.7

Bw, body weight; HDC + SCT, high dose chemotherapy + stem cell transplantation.
[a]One donation of antibiotic = the dose of each compound that has been applied according to the recommendation per day.
[b]Mean numbers of donations of erythrocyte/thrombocyte concentrates per 100 days or donations of antibiotics per treated patient per 100 days.

non-infectious disorders and reflect the incidence of B19V-infection in children [5,20]. This is, however, in contrast to haematological (group A, 8/11 patients, 72.2%) and oncological patients (group B, 17/31 patients, 54.8%), who displayed significantly higher values for DNA prevalence in seropositive patients ($p < 0.001$).

Due to the destruction of erythroid precursors during acute infection, patients with underlying haematological diseases are at risk of developing severe anaemia, transient aplastic crisis and reticulocytopenia. As a consequence, B19V-DNA was detected most frequently in children with non-malignant haematological diseases. In context with acute B19V-infection, Fanconi anaemia became apparent in patients A2 and A3 and patient A4 developed clinically apparent aplastic anaemia without an underlying condition. Furthermore, B19V-infection is known to cause thrombocytopenia and to trigger autoimmune disorders [5,20–24]. We observed markers for acute or recent B19V-infection in five patients presenting with autoimmune disease: ITP was diagnosed in patients AI and AII, Kawasaki-disease in patient AIII, thrombocytopenia in patient AIV and Evan's syndrome in patient A1, even though, contraversially, Kawasaki-disease and Evan's syndrome have been associated with B19V-infection [25–27].

Following acute B19V-infection transient neutropenia and pancytopenia may be established and the reduced immune control may be responsible for the appearance of underlying malignant diseases [1,2]. Furthermore B19V-replication leads to the destruction of erythroid precursors followed by a massive proliferation of reticulocytes in bone marrow [1]. Also this situation may affect the division of residual tumour cells and explain the frequent detection of B19V-DNA in 13/68 patients (19.1%) with malignancies at the time of admission. B19V-DNA was detectable in six patients with solid tumours. In patient B5 (a child successfully treated previously) acute B19V-infection was associated with an ALL-relapse. As acute B19V-infection has been described to precede ALL [28–31], it may be assumed that it also triggered this ALL-relapse. Combined with markers for previous B19V infection, ALL-patients B1, B3 and BI displayed low-level viraemia. Erythrocyte transfusions had been applied to patient B1 1 day, and to patient B3 3 months, prior to hospital admission and serum acquisition in the present study. As back-up samples were not available, it is unclear whether B19V was acquired via natural infection or transfusion. Alternatively, recent infection or reactivation of latent B19V-DNA may be responsible for this finding. In ALL/AML-patients B2, B4, B5 and B7, B19V-DNA was first observed during maintenance chemotherapy. All four patients were treated with erythrocyte and/or thrombocyte transfusions combined with additional blood products (albumin, IVIG). As B19V is a frequent contaminant of blood and blood products this finding raises the suspicion of iatrogenic transmission.

In B19V-DNA-positive cancer patients, courses of neoplastic disease were more severe and associated with higher number of relapses. The therapeutic supportive regimen required more erythrocyte and thrombocyte transfusions (Table 3). Neutropenia and lymphocytosis combined with reduced haemoglobin levels and red blood cell counts in B19V-DNA-positive paediatric leukaemia patients have been also described by Zaki and co-workers [32,33]. Recent publications report that B19V-DNA-positive ALL-patients required more blood transfusions than B19V-DNA-negative ALL-patients [8,10,27]. As our study included patients with malignant lymphoma and solid tumours we could show that the necessity for enhanced administration of blood cells and of antibiotics over extended periods is not only observed with leukaemia.

B19V-infection was shown to be an important cause of anaemia and cytopenia in children with haematological and/or oncological diseases. In patients with unexplained cytopenia, B19V-infection should be considered and diagnostically confirmed. In B19V-DNA-positive leukaemia and solid tumour patients, treatment was associated with complications that required more blood transfusions and courses of antibiotics. Frequent blood transfusions are not only associated with high costs, however, but also involve the additional risk of transferring infections. Due to these problems measures to avoid iatrogenic or nosocomial B19V transmission have to be undertaken.

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Transparency declaration

There is no conflict of interests for any of the authors.

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